

Supplement:

Role of intravenous ketamine in the pathogenesis of secondary sclerosing cholangitis in critically ill patients: perpetrator or innocent bystander?

Answers provided by forensic toxicology

Supplementary Table 1 Patient data and results of toxicological analyses.

Patient Number	1	2	3	4	5	6	7	8	9	10
Patient data										
Age (years)	53	34	58	58	44	61	30	64	59	61
Gender	f	m	m	m	m	m	m	f	m	m
Cumulative ketamine dose (gram)	19	24	6	77	30	26	115	37	148	12
ICU day of ...										
Intubation	1	1	1	1	1	1	1	1	1	1
Cholestasis onset*	10	7	7	9	3	6	5	2	5	6
First dose of ketamine	11	6	1	1	1	2	5	14	15	2
Last dose of ketamine	15	28	26	16	11	7	32	50	63	6
ERC with cast removal	59	39	72	290	107	77	257	91	528	106
Cholestasis onset prior to start of ketamine?	yes	no	no	no	no	no	yes	yes	yes	no
Time between last dose of ketamine and cast removal (days)	44	11	46	274	96	70	225	41	465	100
Toxicological analysis of casts[#]										
Ketamine	+++	+	-	+	-	-	-	-	-	-
Norketamine	++	++	+	-	-	-	+	-	-	-
DHNK	-	+++	+	-	+	+	-	-	-	-
Toxicological analysis of cast surrounding aqueous solution[#]										
Ketamine	+++	+	-	-	++	-	-	+	-	-
Norketamine	++	++	+	-	+	-	-	-	-	-
DHNK	+	+++	+	-	+	+	+	-	-	-

*Onset of cholestasis according to the recommendations of the European Association for the Study of the Liver, EASL: serum alkaline phosphatase higher than 1.5 times the upper limit of normal (ULN) and γ -glutamyltranspeptidase $> 3 \times$ ULN [6], [#]relative concentration compared to detection limit: + low, ++ moderate, +++ high, - not detectable, *DHNK* dehydronorketamine, *ERC* endoscopic retrograde cholangiography, *f* female, *ICU* intensive care unit; *m* male.

Methods

All included patients had been mechanically ventilated for acute respiratory distress syndrome (ARDS), nine of them for COVID-19-associated ARDS and one patient for non-COVID-19 ARDS. For analysis, approximately 30 mg casts and 200 μ l of the appropriate aqueous medium were extracted using ethyl acetate/dichloromethane (85/15, v/v), evaporated to dryness and reconstituted in 100 μ l acetonitrile/water (50/50, v/v). Non-target screening for the detection of drugs and pharmaceuticals was accomplished using high-resolution quadrupole time-of-flight analysis (Q-TOF). Additionally, targeted quantification of ketamine was performed by a standard addition approach using LC-tandem mass spectrometry. Method limits of detection (LOD) for ketamine were evaluated by appropriate matrix matched dilutions of sample materials via signal-to-noise ratio (S/N) determination. For the surrounding aqueous solution, a LOD of 7.5 pg/ml was calculated; for casts a LOD of 0.07 pg/mg was determined.